DM SHORT REPORT

Human Insulin Analogue [LYS(B28), PRO(B29)]: The Ideal Pump Insulin?

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The short-acting insulin analogue lispro ([LYS(B28), PRO(B29)] is absorbed from the subcutis more rapidly than soluble insulin (S). To compare the clinical effectiveness of lispro vs S, 11 Type 1 patients using continuous subcutaneous insulin infusion (CSII) therapy (6 F, 5 M, age 30 ± 2.5 years, diabetes duration 14 ± 1.0 years, BMI 24.0 ± 0.8 kg m^{-2}, HbA_{1c} 6.5 ± 0.2 %) were studied in an open, randomized, crossover study for 6 months (3 months lispro and 3 months S or vice versa). During lispro treatment mean fasting and 2 h postprandial blood glucose were lower compared to the S phase (fasting 6.5 ± 0.4 vs 7.5 ± 0.4 mmol l^{-1} (NS), postprandial 6.8 ± 0.3 vs 8.3 ± 0.3 mmol l^{-1}, $p = 0.03$). In patients treated first with lispro HbA_{1c} levels improved from 6.3 ± 0.2 % to 5.7 ± 0.3 %; On reversion to S HbA_{1c} increased to 6.2 ± 0.2 %. In the group treated first with S, HbA_{1c} fell (6.7 ± 0.4 % vs 6.5 ± 0.3 %) and then improved further to 6.3 ± 0.3% with lispro. None of these changes were significant. There was no significant difference with respect to hypoglycaemic or other adverse events. It can be concluded that lispro in CSII therapy is safe and may improve postprandial glucose excursions. © **1998 John Wiley & Sons, Ltd.**

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Introduction

In Type 1 diabetes mellitus, intensified insulin treatment and especially continuous subcutaneous insulin infusion (CSII) are considered useful therapeutic options to establish long-term optimal metabolic control.[1] However after subcutaneous injection of soluble insulin, the plasma concentration of insulin peaks later and remains elevated longer than occurs with physiological insulin release into the portal system in healthy subjects.[2] This time–action profile results from the self-association of soluble insulin into dimers, tetramers and hexamers retarding and prolonging its entry into the blood stream.[2–5,11] Insulin lispro is an insulin analogue with reversal of the amino-acid sequence at position 28 and 29 of the β-chair. This modification leads to less self-association[6,11] resulting in a more rapid absorption and an altered time–action profile which is more physiological than that of conventional soluble insulin.[7–12] Consequently, the insulin can be injected immediately prior to meals and both postprandial blood glucose peaks and the risk of hypoglycaemia are lower.[9,10]

Lispro insulin incorporated into therapy might be better able to mimic physiological insulin blood profiles over a 24 h period. The clinical safety and efficacy of lispro insulin versus conventional human soluble insulin in CSII treatment was studied in well-controlled Type 1 diabetic patients.

Patients and Methods

Eleven patients from one centre were included in the trial (6 female, 5 male; age 30 ± 2.5 years; duration of diabetes 14 ± 1.0 years; BMI 24 ± 1 kg m^{-2}). The inclusion criteria were Type 1 diabetes, age between 18 and 65 years, use of intensified insulin therapy for at least 2 years, with CSII (H-Tron V 100, Disetronic®, Germany) therapy for at least 6 months prior to the study. Patients with known allergy to insulin, severe complications of diabetes, inadequate metabolic control (HbA_{1c}>10 %), life-threatening diseases or drug abuse were excluded. Pregnant women or women who intended to become pregnant during the study were not accepted. All patients gave written consent. The study was approved by the local Ethics Review Committee.

After a run-in period of 4 weeks, the patients were randomized either to continue their pump therapy with human soluble insulin (Humulin S®) or to use insulin lispro (Humalog®). Insulin was infused into the subcutis of the abdomen throughout the study. The infusion site was changed at 24–48 h intervals. Soluble insulin boluses were given 30 min prior to meals while insulin lispro boluses were given immediately before the main meals, i.e. breakfast, lunch, and dinner. After a treatment period of 3 months, patients converted to the alternative insulin for another 3 months. During the study the patients were seen eight times. At visit 2 (end of run-in), 5 (crossover)

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and 8 (end of the study) records were made of: HbA_{1c} levels, blood glucose profiles over the previous 3 days, weight, basal and meal-related insulin doses, and replies to a quality of life questionnaire (concerning health distress, treatment satisfaction and treatment flexibility). The number of hypoglycaemic episodes (defined as a blood glucose level <3.5 mmol l^{-1} and/or subjective signs or symptoms of hypoglycaemia) and adverse events were registered at each visit.

HbA_{1c} was measured by a HPLC method (Biorad®, Germany). The non-diabetic range is quoted as between 4.0 and 6.0 %.

All patients used Accutrend DM meters and test strips (Boehringer, Germany) to monitor their capillary blood glucose. The accuracy of the tests was validated at regular intervals against the reference laboratory method.

Analysis of variance with repeated measurements (BMDP-Software) was applied to evaluate the influence of group and time on continuous variables (blood glucose, HbA_{1c}, insulin dose). Wilcoxon rank sum test was used to test the differences in the number of hypoglycaemic episodes. All results are given as mean ± SEM.

Results

All the patients completed the study in accordance with the protocol and no severe adverse events were registered. Fasting blood glucose as well as basal and bolus insulin requirements were not significantly different during the two treatment periods (Table 1). Hypoglycaemic episodes were similar during human regular insulin and insulin lispro (Table 1). There were no severe episodes requiring external help with either intravenous glucose or glucagon infusion. There were no episodes of ketosis. The 2 h postprandial blood glucose was significantly lower during treatment with insulin lispro (Table 1). The time course of HbA_{1c} is summarized in Figure 1. Mean HbA_{1c} levels did not differ significantly between the groups at the time of randomization (visit 2): 6.3 ± 0.2 % versus 6.7 ± 0.4 %. In patients treated first with lispro, HbA_{1c} levels decreased to 5.7 ± 0.3% (NS) at 3 months and increased again to 6.2 ± 0.2 % (NS) 3 months after reverting to conventional soluble insulin. HbA_{1c} also decreased in the patients treated first with soluble insulin from 6.7 ± 0.4 % to 6.5 ± 0.3 % (NS) and decreased further to 6.3 ± 0.3 % (NS) at the end of the lispro period. There was no change in the body mass index during the study. No significant difference concerning treatment satisfaction was noted. However, all patients decided to continue their therapy with lispro, apparently because of its greater flexibility.

Table 1. Blood glucose, insulin dose, and hypoglycemic episodes

	Lispro	Regular	*P*-value
Fasting blood glucose (mmol l^{-1})	6.5 ± 0.4	7.5 ± 0.4	NS
2 h postprandial blood glucose (mmol l^{-1})	6.8 ± 0.3	8.3 ± 0.3	0.03
Basal insulin (IU day^{-1})	19 ± 2	20 ± 1	NS
Bolus insulin (IU $12g^{-1}$ carbohydrates)	1.4 ± 0.1	1.5 ± 0.1	NS
Hypoglycaemic episodes per 30 days	4 ± 0.9	3.2 ± 0.7	NS

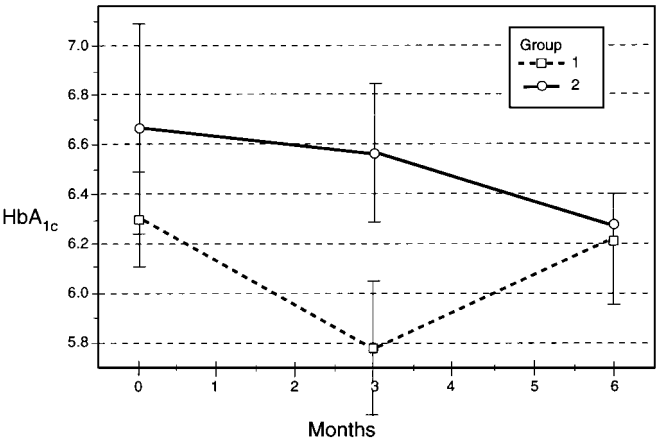

Figure 1. Time course of HbA_{1C} values; mean ± SEM. Group 1: first insulin lispro followed by regular insulin. Group 2: first regular insulin then insulin lispro

Discussion

Although a number of short-acting insulin analogues have been synthesized, only a few have been shown so far to be suitable for clinical use.[13,14] Of these lispro insulin has been shown in a number of recent studies to have the most appropriate pharmacokinetics.[15] No differences have been reported between conventional human soluble insulin and insulin lispro with respect to the likelihood of allergical reactions, adverse events, immunogenicity and abnormal laboratory findings.[16–18]

Recent large scale clinical trials of insulin lispro in the treatment of Type 1 and Type 2 diabetic patients have assessed its biological efficacy. However there is only one study looking at insulin lispro in CSII. This study used a similar experimental design than ours except that both soluble insulin and lispro were injected as premeal boluses 0–5 min prior to each main meal,[19] allowing a double-blind crossover design. While preprandial, bedtime, and 2 h am values for blood glucose were not significantly different, the 1 h postprandial blood glucose was much lower with insulin lispro compared with soluble insulin.[19] This is consistent with our data in which 2 h postprandial blood glucose levels were lower on lispro, given as recommended immediately before eating while conventional soluble insulin was given also as recommended, 30 min before meals. It is important to note that in intensified therapy with multiple daily infections,[20] preprandial glucose levels may be higher on lispro. That this did not happen with CSII

reflects the effect of the basal infusion and suggests CSII may be an optimal way to deliver the new insulin. It is perhaps disappointing that, despite this, the change in glycosylated haemoglobin during insulin lispro treatment similar to the Canadian study,[19] was not significant. The starting values were much lower in our patients, and it may be that this, together with the small number of patients studied, limited our ability to detect improvement. It is important to stress that even so, with very strict metabolic control, there was not a high frequency of hypoglycaemia. Our data are in agreement with other studies using insulin lispro in CSII as well as in other forms of intensified insulin treatment.[9,10,19] In the earlier study, insulin precipitations in the reservoir or the pump catheter was reported twice for each insulin.[19] In our study, this did not occur. In one study insulin lispro was stable in pumps for at least 48 h.[21] It is probably necessary to inform patients of the possibility of insulin precipitation when daily insulin requirement is low and insulin remains in the pump cartridges for longer than this.

Lispro insulin appears to have a measurable impact on lifestyle benefits in Type 1 diabetic patients;[22] quality of life using different scales however were not significantly different between regular insulin and insulin lispro.[21] In our study, we could not find significant differences in quality of life but all patients wanted to continue their CSII with insulin lispro.

We conclude that insulin lispro results in good long-term metabolic control without a higher risk of hypoglycaemia, ketoacidosis or other adverse events in CSII.

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